氏　　名	AKA EBOUKELE
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論文審査委員（主査）	木村　和子（自然科学研究科・教授）
論文審査委員（副査）	松下　　良（自然科学研究科・助教授）， 早川　和一（自然科学研究科・教授）， 垣内　信子（自然科学研究科・助教授）， 古川　裕之（医学部附属病院・助教授）

"Assessment of counterfeit medicines by authenticity investigation in the pharmaceutical market of Côte d'Ivoire"

By AKA Eboukele

EXECUTIVE SUMMARY

1 Background:

Medicines play an important role in saving lives, restoring health, preventing diseases and stopping epidemics. But, to achieve these goals, medicines must be safe, effective, accessible and of good quality, and used appropriately. However, recently, the availability of counterfeit drugs has been increasing exponentially worldwide, due to the growth in international and regional free trade, high demand for curative and preventive drugs, proliferation of small pharmaceutical companies, and inadequate drug regulation in many countries. Almost all kinds of pharmaceuticals may be counterfeited, but, in developing countries, essential drugs used to treat life-threatening diseases, such as antibiotics and antiparasitics, are often involved. Besides, in these countries, counterfeit and substandard drugs are particularly common in the flourishing illegitimate pharmaceutical outlets, supported by the people's needs in conjunction with extreme poverty.

According to the World Health Organization (WHO) a counterfeit medicine is "a medicine which is deliberately and fraudulently mislabeled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeit products may include products with correct ingredients, wrong ingredients, without active ingredients, with the incorrect quantity of active ingredients or with fake packaging". In accordance with this definition, what makes a medicine counterfeit is the deliberate or intentional nature of the mislabeling of a product to deceive the consumers. In contrast, substandard medicines are products whose composition and ingredients do not meet the correct scientific specifications and which are consequently ineffective and often dangerous for the patient. Substandard products may occur as a result of negligence, human errors, insufficient human and financial resources or counterfeiting.

So far most surveys on counterfeit medicines were limited to laboratory testing, with no or insufficient attempt to elucidate the causes for the medicines to be of poor quality, or to investigate the actual sources and origins of the medicines, so as to distinguish between counterfeit and genuine medicines.

In various regions of the world such as Southeast Asia, many initiatives have been undertaken to identify the situations and carry out countermeasures. Unlikely, the studies conducted to assess the situation in Africa are related to a limited number of countries.

In Côte d'Ivoire, no study has been conducted so far to valuate the counterfeit medicines circulating in the country and no reliable data of the scale of the phenomenon are currently available. This matter of fact has motivated the choice of Côte d'Ivoire i) to establish **for the first time** the methodology of authenticity investigation in its comprehensive aspects as recommended by the WHO, ii) to assess the prevalence of counterfeit medicines circulating in both the legal and the illegal pharmaceutical market, by the mean of authenticity investigation, and thereby, demonstrate the effectiveness of the authenticity investigation in the detection of counterfeit medicines, iii) to assess the quality of medicines available in the pharmaceutical market.

2 Methods

2.1. Sampling areas

Four cities in Côte d'Ivoire (15.4 M inhbts) were chosen for the collection of the samples:Abidjan 2.9 M inhbts, Gagnoa 0.1 M inhbts , Yamoussoukro (capital city) 0.3 M inhbts, San Pedro 0.1 M inhbts. The reasons of the selection of these cities are as follows:

- Abidjan, commercial center in Côte d'Ivoire, for the size of the informal pharmaceutical market places that it shelters
- San Pedro, for the existence in this city of the largest shantytown in West Africa, and also for its proximity to the neighboring country Liberia in war for more than twenty years, a favourable condition to drug counterfeiting
- Gagnoa and Yamoussoukro, for their high prevalence of counterfeit medicines in the past.

2.2. Sample collection

Following the WHO criteria, the samples to be collected were selected among the essential medicine list of Côte d'Ivoire, the most widely used, the therapeutically important and the most likely to be counterfeited. Accordingly, the antibiotics (amoxicillin, ampicillin, cotrimoxazol), the antiparasitics (albendazole, mebendazole, chloroquine, amodiaquine, sulfadoxin-pyrimethamine, metronidazole) and the antipyretics (paracetamol) were chosen to be collected.

Sample collection

Samples were purchased from 3rd to 12th July 2004 by a team of 3 native pharmacy workers led by a pharmacist (the author), from the street pharmaceutical markets of 4 cities in the Côte d'Ivoire (Abidjan, Gagnoa, Yamoussoukro, San Pedro). The medicines were purchased from sellers who either were ambulatory or had a fixed stall on the street or in the market place. The selection of the vendors was made randomly. Medicines collected from the same outlet with the labeling showing the same mentions of International Non proprietary Name (INN), brand name, manufacturer/marketer name and address, strength, form and batch/lot number were considered as one sample For the purpose of authenticity investigation, the medicines were required to be sold with their outer containers (boxes or plastic bags), or at least with their blisters, providing minimum information about the batch/lot number and the manufacturer or marketer. Only solid oral forms (capsules or tablets) were collected, in a sufficient amount (minimum 3 units,

maximum 100 units) for experiments and authenticity investigation purposes. All the samples were kept at room temperature until analysis and authenticity investigation.

Immediately after it was bought, each sample was sealed in an airtight plastic bag on which a code was assigned and stuck. A "Sample Information Sheet" was duly filled out and attached to each sample's container as soon as its codification was made. This record sheet provides information about the sample code, the INN and strength, the brand name, the manufacturer name and address, the price, the batch or lot number, the manufacturing and expiry date, the package size (number of units), the quantity purchased and the date and place of collection. All the samples were kept at room temperature until analysis and authenticity investigation.

2.3 Authenticity investigation

2.3.1. Organoleptic descriptions of the samples

Through a close observation of each pharmaceutical preparation, detailed organoleptic descriptions of the outer containers, the blisters, the package inserts and the dosage forms (capsules or tablets) were prepared for each sample. Moreover, other important mentions such as the manufacturing and expiry dates, the registration and the batch/lot numbers, the bar code, the indications and cautions, the storage conditions were recorded. To have a better illustration of the described items, we scanned the products in their entire parts (boxes, blisters, dosage forms, package inserts), so as to make the pictures and the inscriptions on each side of the sample as clear as possible. All these data were then compiled in a document so named "catalogue of the sample". At the end of this document a comment sheet was added to gather the manufacturers' viewpoints about the description of the samples we made.

2.3.2. Correspondences with the drug authorities and the manufacturers

The "catalogues of samples" were sent by registered mail along with actual sample(s) and specific questionnaires to both the MRA of the manufacturing country and the labeled pharmaceutical companies. Substantially, the MRAs were asked i) to check whether the labeled company was licensed as a pharmaceutical manufacturer or pharmaceutical marketer or not, according to the pharmaceutical law in effect in their countries; ii) to check whether the pharmaceutical sample was registered or authorized under the pharmaceutical law in their countries. The manufacturers were asked i) to check the genuineness of the sample (genuineness means that the product was actually made by the manufacturer on the label) and, ii) to provide information (if any) about the possible counterfeiter, in case the product was not a genuine one.

2.3.3. Follow-up

A comprehensive repertory of contacts (mailing addresses, e-mails, telephone and fax numbers) of all the involved MRAs and manufacturers was made beforehand. The follow-up was carried out by constant communications with the concerned parties, using all the above mentioned means to get answered and to gather information. By this way, we could make sure that the addressees duly received our sending, correctly understood our inquiries, and were willing to reply us. Further explanations about the purpose of the study were provided when necessary, in a way to convince them to cooperate.

All the follow-up steps and results were compiled in an Access data base as soon as we received them, for an easy analysis and interpretation.

2.4 Sample analysis

A primary quality screening of the samples by The Thin Layer Chromatogram (TLC) was performed on one tablet or capsule of each collected sample for the identification of active ingredients, at the National Laboratory of Public Health in Abidjan.

The developing solvents and standard solutions were prepared according to the method developed by JICWELS. The standard solutions were prepared with reagent grade active ingredients purchased from the commerce.

The samples were further analyzed by HPLC in our Laboratory (Kanazawa University), to determine their content of active ingredient(s). The HPLC analyses were substantially performed following the US Pharmacopoeia (USP XXVII edition) and Japanese Pharmacopoeia (XIV edition). The standard and sample solutions were obtained by dissolving the equivalent of 10 mg of the active principle in the dissolution solvent and diluting to a concentration of 0.4 mg/mL. In each case, the standard solutions were again diluted with the mobile phases to concentrations of 0.2, 0.1, 0.05, 0.025 mg/ml to generate calibration curves. The sample solutions were also diluted with the mobile phases to a final concentration of 0.1 mg/ml, and 20 µl aliquots were injected into the HPLC columns at a flow rate of 0.8 ml/min and at a column temperature of 30°C. The UV detector was set at a different length according to the product. All the samples were analyzed three times, using a different tablet for each test, to assess the possible intra-sample variations. Moreover, the samples were injected in duplicate to confirm the reproducibility. Mean values of active ingredient contents were recorded for each sample and compared with the limits specified by the pharmacopoeias.

2.5 Data interpretation

Based on the answers obtained from the authenticity investigation, a sample could be stated as genuine or counterfeit. These results were further crossed with those of the laboratory tests. Accordingly, four categories of medicines were identified: genuine medicines passed laboratory tests, genuine medicines failed laboratory tests, and counterfeit medicines passed laboratory tests and counterfeit medicines failed laboratory (Figure1).

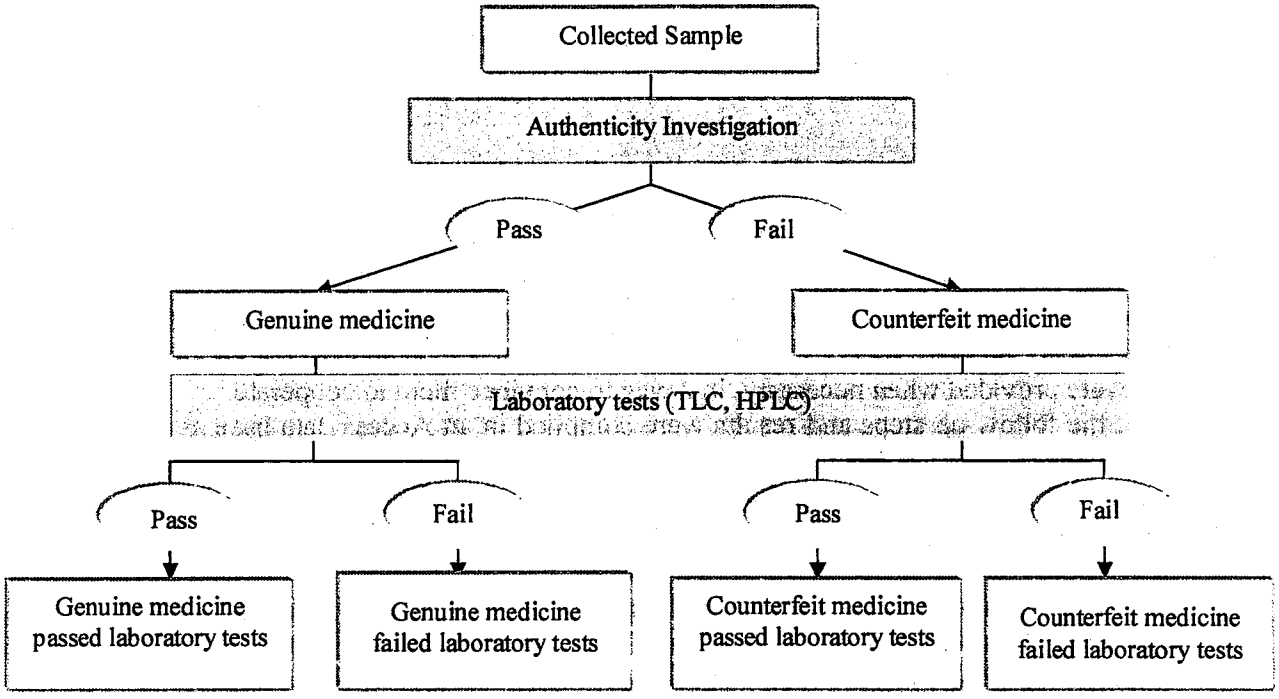

Figure 1: Decision tree for the classification of the medicines
TLC = thin-layer chromatography; HPLC = high-performance liquid chromatography

3 Results

3-1 Description of the samples

From the 4 cities visited, a total of 353 samples were collected, of which, 83% (293/353) were bought in the street markets and 17% (60/353) in the legal pharmacies.

The collected samples belong to the 3 therapeutic classes of antiparasitics (41 %), antipyretics (39%), and antibiotics (20%) (Fugre 2).

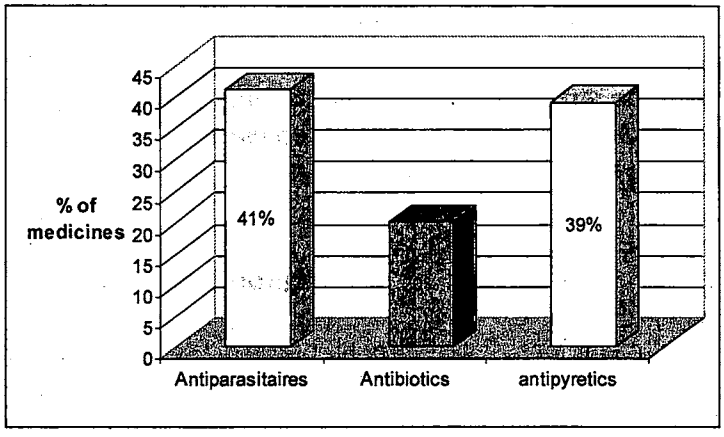

Figure 2: Distribution of medicines by therapeutic classes

Compare to the legal pharmacies, the means of prices of medicines in the street market is 49 FCFA, while in the legal pharmacies it is 269 FCFA, 5 times higher than the first one. 92 % (325/353) of the total samples are imported from 11 countries, with nearly half (49%) from India. Only 8% (28/353) are domestically produced. 79% (278/353) of the samples were not registered in Côte d'Ivoire and all of them were imported medicines, exclusively sampled from the street markets. Regarding the registration status of samples in the pharmaceutical markets, 5% (15/293) of the medicines collected in the street market were registered, and 100% (60/60) of those collected in the legal pharmacies were registered.

3-2 Authenticity investigation

We succeeded in receiving 75% (60/80) of "**replies**" and 25% (20/80) of "**no replies**" from the total enquiries sent to Medicine Regulatory Authorities, MRAs (12) and pharmaceutical companies (68). The authenticity investigation revealed that 14% (51/353) of the collected samples were counterfeit medicines. Counterfeit medicines were found in both outlets, with a significantly higher proportion of 96% in the illegal street markets. 21% (29/139) of counterfeit medicines were detected among the antipyretics, 14% (20/144) among the antiparasitics, and 3% (2/70) were detected among the antibiotics. Counterfeit medicines were detected in both illegal and legal outlets. Indeed, 96% (49/51) of the counterfeit medicines were sampled in the street markets, whilst 4% (2/51) were collected in legal pharmacies. However, there is a significantly higher proportion of counterfeit medicines among the samples collected in the street market 17% (49/293), than counterfeit medicines among the samples collected in the legal pharmacies 3% (2/60). 94% (48/51) of the detected counterfeit medicines were claimed to originate from India, and 6% (3/51) from China. 4 specific types of counterfeit medicines that were identified including 8% (4/51) of the type A (medicines with identity usurpation), 22% (11/51) of the Type B (medicines bearing false or illegal mentions about the source), 10% (5/51) of the Type C (medicines bearing false registration numbers), 41% (21/51) of the Type D (deceptively similar and look-alike medicines), 18% (9/51) combining the counterfeiting types B and D, and 2% (1/51) combining the types B, C and D.

3-3 Laboratory tests

The laboratory tests revealed that 28% (92/353) of the samples do not contain the correct amount of active ingredients, of which 16% (15/92) were collected from the legal pharmacies and 84% (77/92) from the street markets. Medicines that failed HPLC tests were found in all the 3 therapeutic classes: the antiparasitics represent 61% (56/92), the antibiotics 22% (20/92) and the antipyretics 17% (16/92).

3-4 Comparison of the results of authenticity investigation combined with laboratory tests

Both counterfeit and genuine medicines failed the laboratory tests. However, a statistically significant rate of 84% (43/51) of counterfeit medicines was revealed to contain the correct amount of active ingredient, compare to a rate of 67% for the genuine ones (Table 1).

Therapeutic classes	INN	Number of samples	Genuine			Counterfeit			Unknown		
			Passed lab tests	Failed lab tests	N/A	Passed lab tests	Failed lab tests	N/A	Passed lab tests	Failed lab tests	N/A
Antiparasitics	Albendazole	25	17	1	5	1	1				
	Amodiaquine	6	6								
	Chloroquine	54	6	41		3	1			3	
	Mebendazole	35	25	1		9					
	Metronidazole	12	9	3							
	Sulfadoxine/ Pyrimethamine	12	4	1		2	3		1	1	
	Sub-total 1	**144**	**67**	**47**	**5**	**15**	**5**	**0**	**1**	**4**	**0**
Antibiotics	Ampicillin	16	10	5		1					
	Amoxicillin	24	17	4					3		
	Sulfamethoxazole / Trimethoprime	30	19	4			1		4	2	
	Sub-total 2	**70**	**46**	**13**	**0**	**1**	**1**	**0**	**7**	**2**	**0**
Analgesics and antipyretics	Paracetamol and combinations	139	63	6		26	3		34	7	
	Sub-total 3	**139**	**63**	**6**	**0**	**26**	**3**	**0**	**34**	**7**	**0**
TOTAL		353	176	66	5	42	9	0	42	13	0

Table 1: Summary of authenticity investigation and laboratory tests

4 Discussions

Through the investigation of their sources and origins, 14% (51/353) of the collected samples were found to be counterfeit. Even though this study was conducted on a limited number of samples with no attempt to be representative of the actual situation in Côte d'Ivoire, these findings give for the first time an accurate reflection of the proportion of counterfeit drugs in a survey, according to the WHO's definition and detection method.

Previous studies estimated that up to 25% of the medicines consumed in developing countries are counterfeit or substandard. However, this study revealed a less proportion (14%) of counterfeit medicines in Côte d'Ivoire, in the limits of the sampling we made. This can suggest that the extent of the phenomenon might be overestimated, due to the frequent confusion between substandard and counterfeit medicines during previous studies.

It has been reported that in developing countries, counterfeit often involves essential medicines used in life-threatening diseases in particular antibiotics and antiparasitics. In accordance with this, counterfeit medicines have been detected in each of the 3 therapeutic classes of antipyretics, antibiotics and antiparasitics that have been selected among the essential medicine list for the study. Counterfeit medicines were most frequently found among antipyretics 21% (29/139), followed by antiparasitics 14% (20/144). Similarly, recent studies have shown that counterfeits of even new antimalarial medicines, such as artesunate and mefloquine, are circulating in Southeast Asia. The high prevalence of various diseases such as malaria, tuberculosis, diarrhea, worm infections, pneumonia, HIV/AIDS, increase the demand for antibiotics and antiparasitics, and thus make it a very attractive target for counterfeiters who benefit from the large amount of products that they easily sell in a short period of time. A higher ratio of counterfeit medicines (17%) has been detected in the street markets, compare to the ones detected in the legal pharmacies (3%). Our results are in accordance with reports stating that in the less-developed countries, counterfeit and substandard medicines are particularly common in the flourishing illegitimate pharmaceutical outlets.

The counterfeit medicines detected were of various types, including products with identity usurpation, products with deceptively similar design with genuine ones ("look-alike" drugs), products bearing false registration numbers, products with factitious or unauthorized manufacturer/marketer name and address. These different forms of counterfeiting are strictly related to the labeling of the medicines and do not involve the quality in terms of contents of active ingredients. Thus, our results suggest that counterfeit medicines detection cannot be based only on laboratory tests, but should include an investigation of the authenticity of the medicines. However, laboratory tests can constitute pertinent clues, especially when the product shows serious quality defects, as it was the cases for one albendazole sample in which no active ingredient was found. Nevertheless, the authenticity investigation of this sample was necessary to state whether this defect was originating from an intentional and fraudulent act or due to a technical error during the manufacturing process.

Most of counterfeit medicines contained the correct amount of active ingredients as specified by the USP. In accordance with these findings, some researchers have reported increasing sophistication of drug counterfeiting. Counterfeit medicines passing laboratory tests, which constitute the largest proportion in our results, seemingly do not represent an immediate threat to public health, unlike substandard medicines. However, as their production and distribution are not within the purview of the medicine regulatory authorities of the country concerned, any associated defect and adverse reactions will not be easily recognized or monitored, and an effective product recall, if needed, would not be possible.

5 Conclusion

We have **for the first time** implemented the methodology of authenticity investigation in its comprehensive aspects as recommended by the WHO. Our findings highlight the fact that counterfeit medicines should not be sought only as worthless medicines, for the counterfeiting activities are more and more sophisticated and the quality of some fake medicines is as good as the genuine ones. Moreover, the types of counterfeiting detected are strictly related to the labeling of the medicines and do not involve the quality in terms of contents of active ingredients. **Thus, our results suggest that counterfeit medicines detection cannot be based only on laboratory tests, but should include an investigation of the authenticity of the medicines.**

To combat more efficiently the counterfeit medicine problem, there is an urgent need for effective regulatory control of pharmaceutical affairs and intellectual property rights.

学位論文審査結果の要旨

発展途上国を中心にカウンターフィットドラッグ（偽造医薬品）の蔓延が懸念されているが、検出法は確立しておらず真の実態は明らかでない。アカエブケル氏は真正性調査によるカウンターフィットドラッグの検出方法を確立するとともに、分析試験の限界を示し、象牙海岸国のカウンターフィットドラッグの蔓延実態を明らかにした：

(i) 象牙海岸国の四市で2004年7月に解熱鎮痛薬、抗寄生虫薬、抗生物質計353サンプルを薬局及び無許可販売業者から収集した。

(ii) 表示上の製造国の薬事当局と製造業者の調査を行い、医薬品の登録、出所起源、業免許を確認することにより、真正性を明らかにする方法を確立した。

(iii) HPLCによる有効成分の確認で、真正医薬品では31％がUSPまたはJPの範囲外であったのに対し、カウンターフィットドラッグでは16%であった。すなわち、これまで一般に行われてきた有効成分確認は、真正性の判定には不適当である。

(iv) 全体のカウンターフィットドラッグ出現率は14%であった。治療区分では解熱鎮痛薬21%、抗寄生虫薬14%、抗生物質3％；業許可区分では薬局3％、無許可販売では17%；医薬品登録では有3％、無18%であった。カウンターフィットドラッグは象牙海岸の医薬品市場に相当程度存在し、特に医薬品規制が履行されていないセクターで多く出現する。

以上のようにアカエブケル氏は、今後のカウンターフィットドラッグ研究に画期的な貢献をなし、博士（薬学）に相当する。